Bio

Biotechnology
Innovation Organization

June 4–5, 2023

#BIO2023
#StandUpForScience

Biotechnology Entrepreneurship Boot Camp

Presented by:

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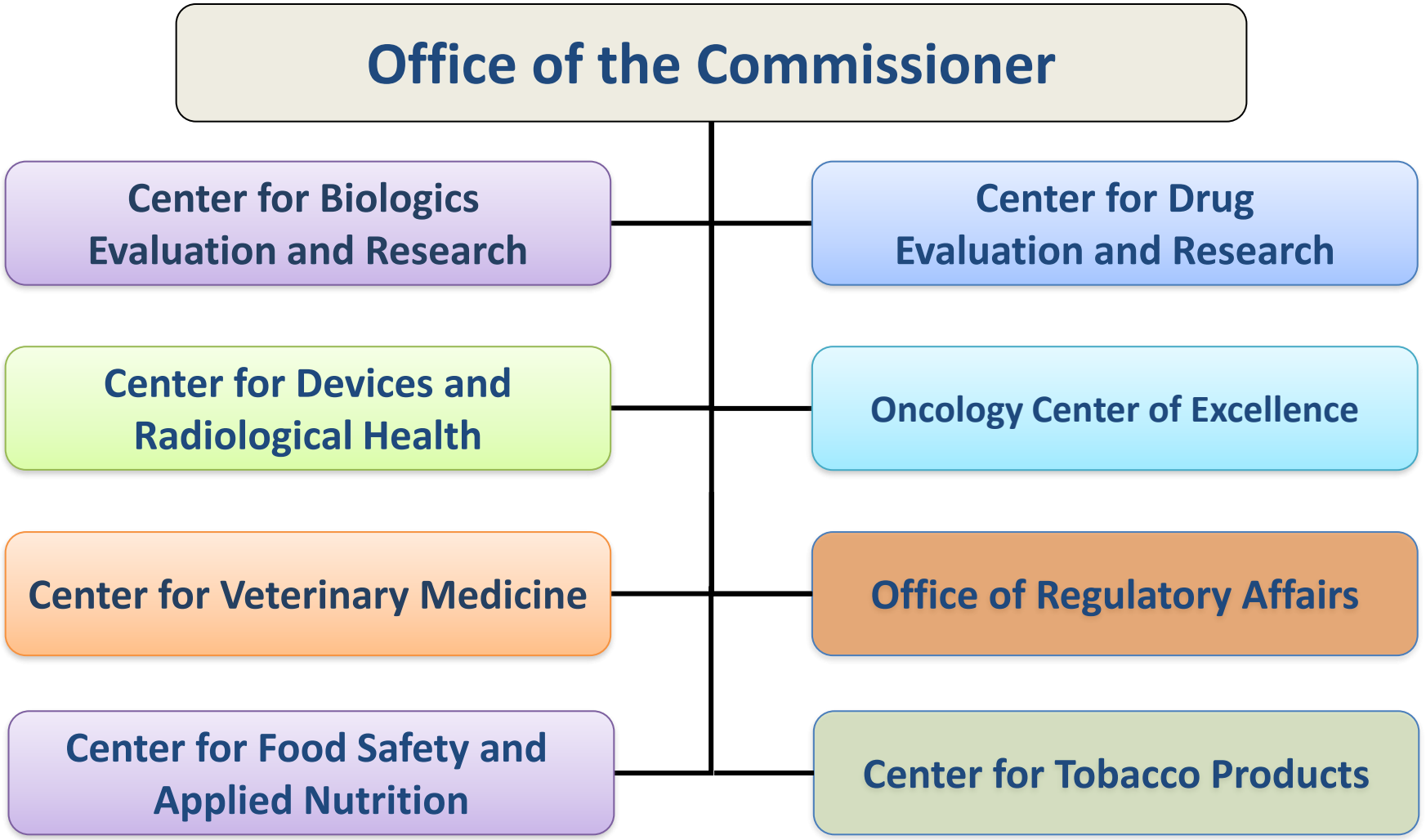
Session 5: Regulatory Planning for the US & Global Market - Implications for Strategy and Financing

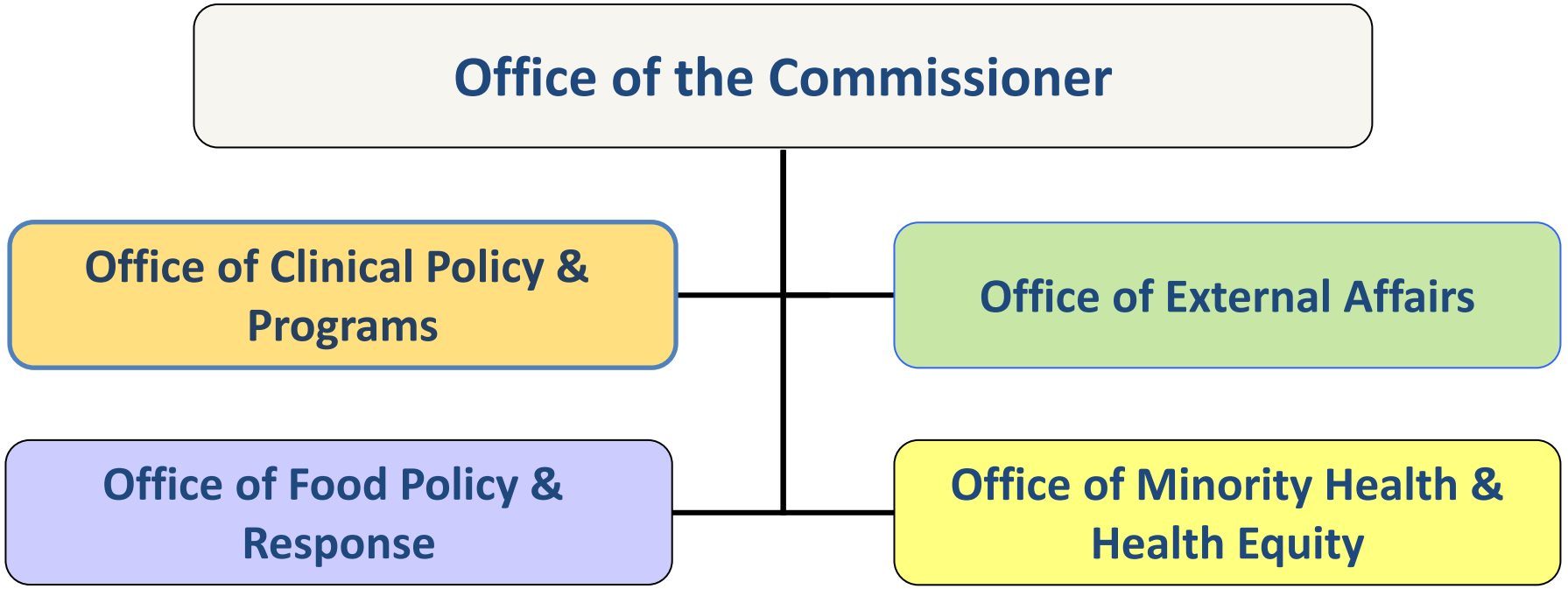

U.S. Food and Drug Administration
Protecting and Promoting Your Health
EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
Australian Government
Department of Health
Therapeutic Goods Administration
MHRA
Who Regulates Medicines?
BfArM
afssaps
Agence française de sécurité sanitaire des produits de santé
CFDA
国家食品药品监督管理总局
China Food and Drug Administration
pmda
独立行政法人
医薬品医療機器総合機構
Pharmaceuticals and Medical Devices Agency

FDA Organization

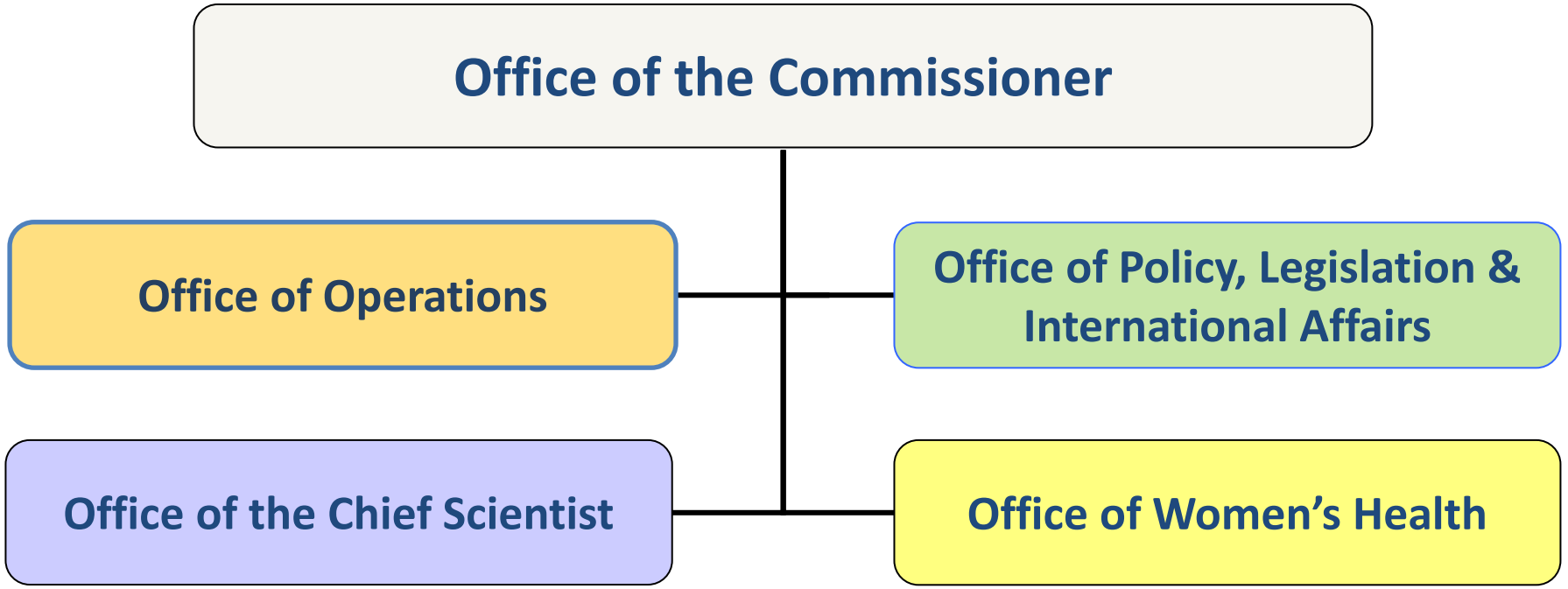


Current as of May 4, 2023

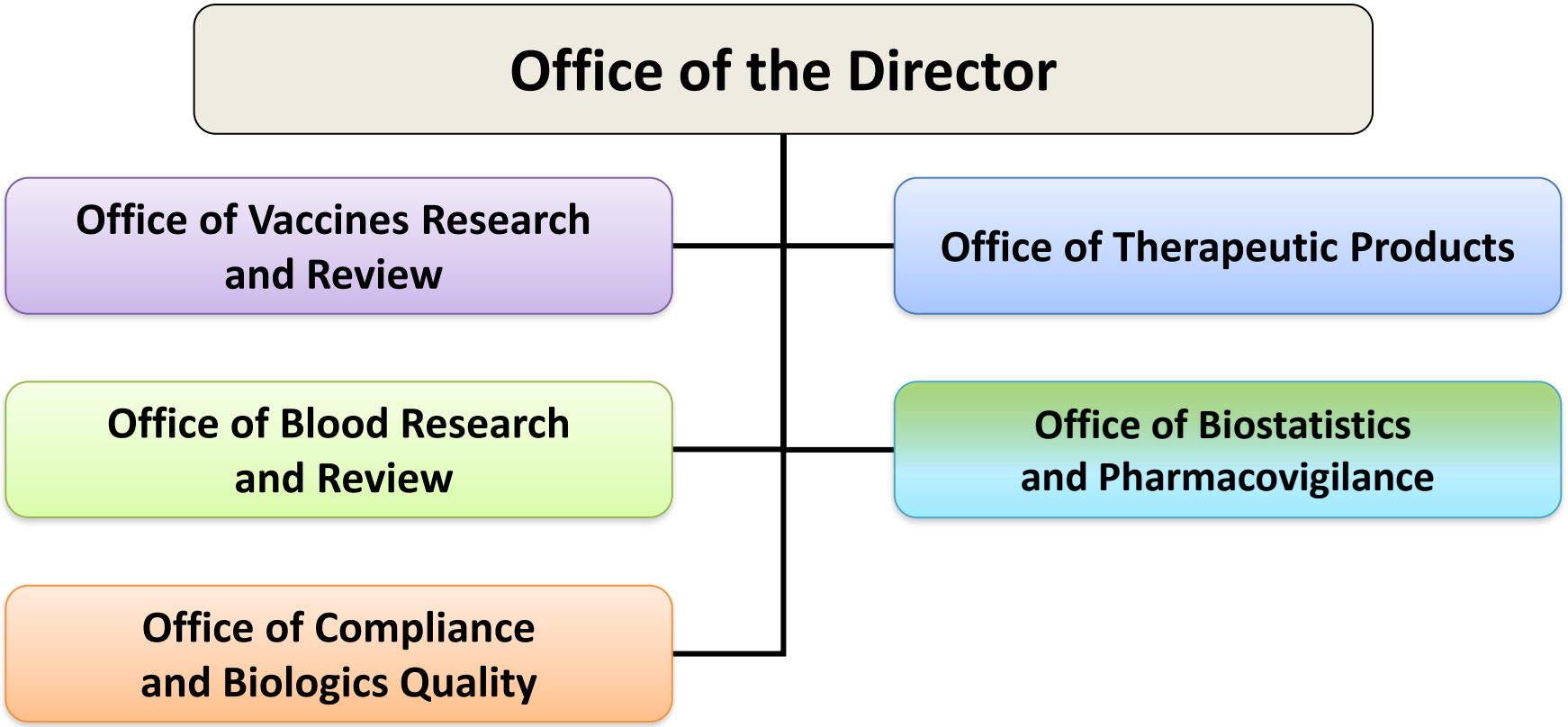
FDA Organization



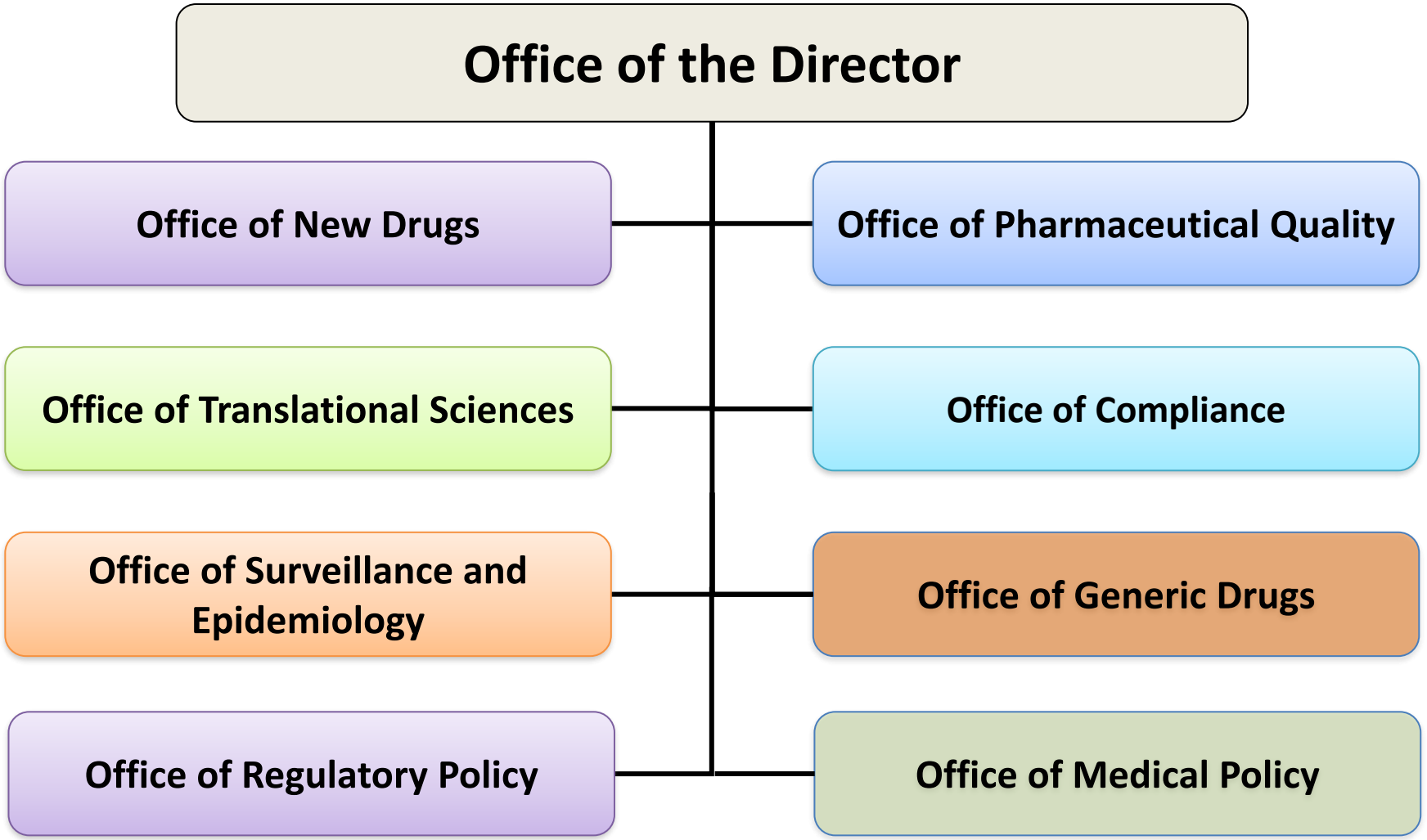
FDA Organization



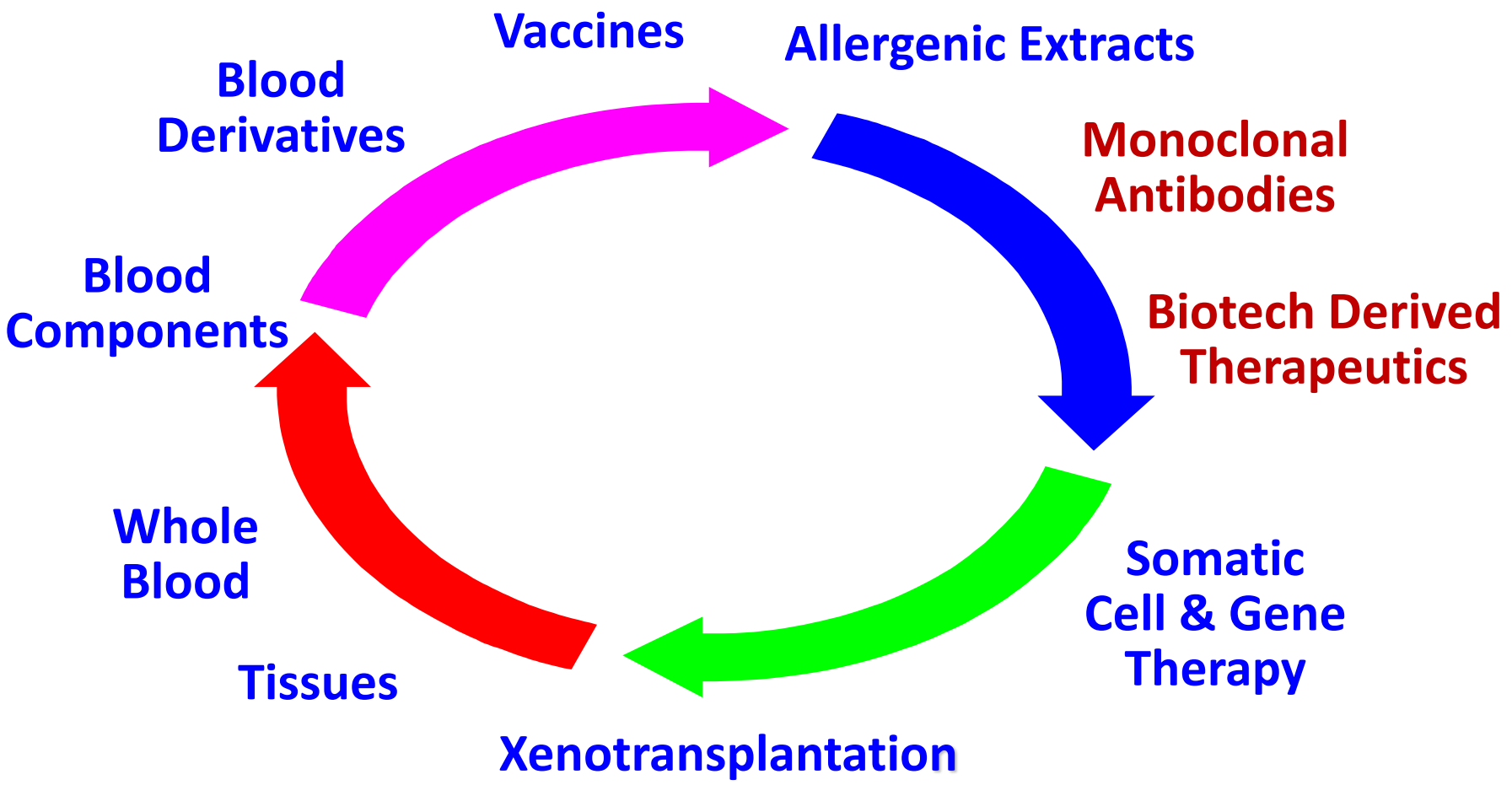
CBER Organization



CDER Organization



BIOLOGICAL PRODUCTS REGULATED BY CBER or CDER



Acts & Regulations Pertinent to Biological Product Development

- PHS Act (42 USC 262-63) Section 351
- FD&C Act (21 USC 301-392)
- Prescription Drug User Fee Act (PDUFA), 1992
  - User fees (application fee, establishment fee, product fee)
- FDAMA, 1997
  - Risk-based review of medical devices
  - Exemption for pharmacy compounding
  - Reauthorization of user fee for drugs
- Public Health Security and Bioterrorism Preparedness and Response Act ("PDUFA III"), 2002
- FDA Amendments Act ("PDUFA IV"), 2007
  - Reauthorization of user fee for drugs and medical devices
  - Reauthorization of Best Pharmaceuticals for Children Act and Pediatric Research Equity Act

Acts & Regulations Pertinent to Biological Product Development

- Biologics Price Competition and Innovation Act, 2009
  - Created path for approval of biosimilars and interchangeable biological products
  - Exclusivity of 12 years for original biological product
  - Exclusivity of 1 year for first interchangeable biosimilar product
  - On March 23, 2020, all biological products approved under a NDA are “deemed” to be a BLA

Acts & Regulations Pertinent to Biological Product Development

- FDA Safety and Innovation Act ("PDUFA V"), 2012
  - User fee for generic drugs, biosimilar drugs
  - Reauthorization of user fee for drugs and medical devices
- FDA Reauthorization Act ("PDUFA VI"), 2017
  - User fee reauthorizations for drugs, medical devices, generics and biosimilars
- FDA User Fee Reauthorization Act ("PDUFA VII"), 2022
  - User fee reauthorizations for drugs, medical devices, generics and biosimilars
  - INTERACT meeting ("Pre-Pre-IND") and Type D meeting in CBER and CDER
  - New allergenics products
  - Use-Related Risk Analysis (URRA) for drug-device and biologics-device combination products

Acts & Regulations Pertinent to Biological Product Development

- 21 CFR
  - 21 CFR 600-680 Biological Product Standards
  - 21 CFR 314.126 Adequate and well-controlled trials
  - 21 CFR 312 Investigational New Drug Application
  - 21 CFR 210-211 Good Manufacturing Practices
  - 21 CFR 4 Regulation of Combination Products
  - 21 CFR 58 Good Laboratory Practices
  - 21 CFR 56 Institutional Review Boards
  - 21 CFR 50 Protection of Human Subjects

Current Regulatory Pathways

- Biologic Products:
  - IND – Investigational New Drug Application (21 CFR 312)
  - BLA – Biologics License Application (21 CFR 600-680)
- Drugs:
  - IND - Investigational New Drug Application (21 CFR 312)
  - NDA – New Drug Application (21 CFR 314)
- Medical Devices:
  - 510(k) – (21 CFR 807)
  - IDE – Investigational Device Exemption (21 CFR 812)
  - PMA – Pre-Market Application (21 CFR 814)

Drug or Biologic -
What difference does it make?

- IND PHASE
  - Identical Regulations for Drugs and Biologics - 21 CFR 312
  - Differences in emphasis and expectations of review divisions
- APPLICATION PHASE
  - DRUGS: New Drug Application (NDA) Regulations - 21 CFR 314
  - BIOLOGICS: Biologics Licensing Regulations - 21 CFR 601
  - Harmonized Application Form - Form 356h; Drugs - NDA; Biologics-BLA
- POST APPROVAL PHASE
  - DRUGS: Inspections, Annual Reports, Manufacturing changes (§ 314.70)
  - BIOLOGICS: Inspections, Lot release, Manufacturing changes (§ 601.12)

Laws, Regulations, Guidance

- LAWS:
  - Public Health Services Act (Biologics)
  - Food, Drug and Cosmetic Act (Drugs)
- REGULATIONS:
  - Code of Federal Regulations (CFR)
  - Proposed rule – Comments – Final rule
  - Title 21 – Food and Drug Administration Regulations
  - 21 CFR 600 – Biological Products : General
- GUIDANCE:
  - Represents FDA current thinking on a specific topic. Does not confer any rights and does not bind the FDA or the company

Therapeutic Biological Products: CDER

- Monoclonal antibodies for in vivo use
- Proteins intended for therapeutic use, including cytokines (e.g. interferons), enzymes (e.g. thrombolytics), and other novel proteins, except for those assigned to CBER (e.g., vaccines and blood products). This category includes therapeutic proteins derived from plants, animals, microorganisms, and recombinant versions of these products
- Immunomodulators (non-vaccine and non-allergenic products intended to treat disease by inhibiting or modifying a pre-existing immune response)
- Growth factors, cytokines, and monoclonal antibodies intended to mobilize, stimulate, decrease or otherwise alter the production of hematopoietic cells in vivo

Therapeutic Biological Products: CBER

- Cellular Products, including products composed of human, bacterial or animal cells …. or from physical parts of those cells
- Gene Therapy Products
- Vaccines
- Allergenic Extracts
- Antitoxins, antivenins, and venoms
- Blood, blood components, plasma derived products including recombinant and transgenic versions of plasma derivatives, blood substitutes, plasma volume expanders, human or animal polyclonal antibody preparations, and certain fibrinolytics such as plasma-derived plasmin, and red cell reagents

TRANSLATIONAL DEVELOPMENT

Discovery Research

Regulated Product Development

Empirical, trial & error, unregulated environment

Structured, highly regulated environment

How to get product into clinical development

- Demonstrate potential clinical usefulness (**early efficacy**)
  - In vitro and / or in vivo (animal) models of disease

- Demonstrate adequate **quality** of product
  - Reproducibly manufacture product
  - Demonstrate purity
  - Formulate into “medicine” – solution, tablet, capsule

- Demonstrate adequate **safety**
  - In vitro and in vivo safety studies
  - Characterize toxicity
  - Justify starting dose and proposed maximum dose

Planning

- Start with an end in mind
  - Product for marketing or
  - Proof of concept

- Develop a basic Target Product Profile
  - Indication
  - Target population
  - Dosage
  - Presentation

Translational Development – Regulatory Challenges

- GLP
- Choice of animal model/species

- GMP

- GCP

- INDs, BLAs, NDAs

Comprehensive Product Development Planning and Management

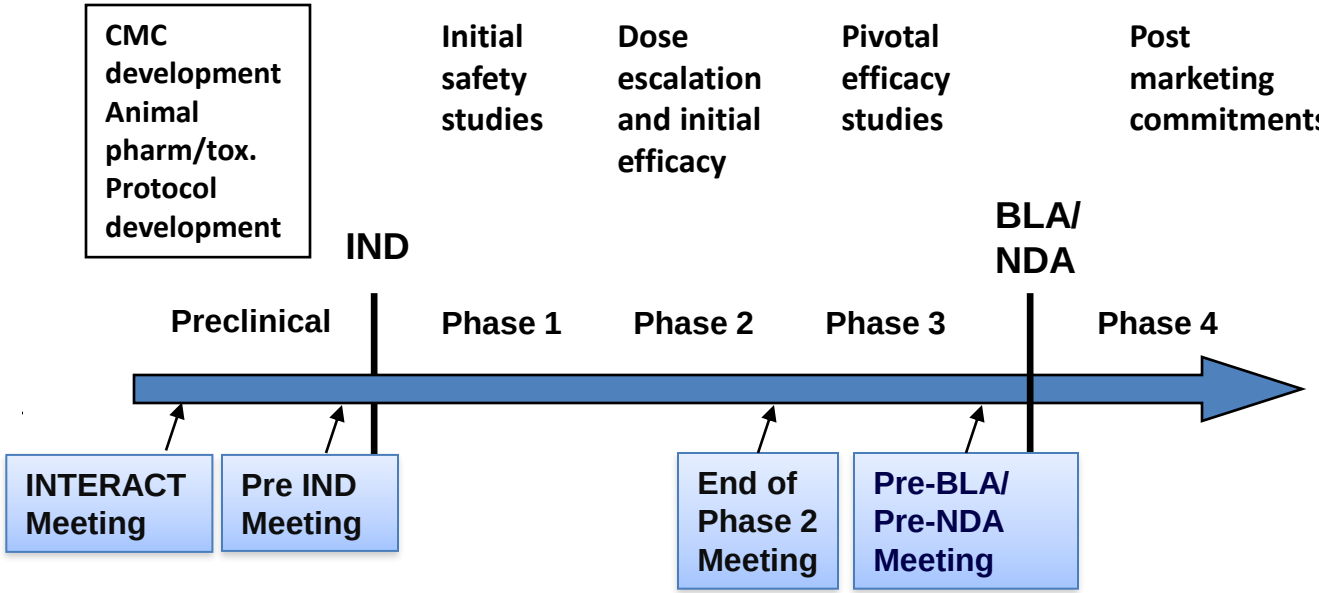
- Gap Analysis of all development areas
- Team approach to development management
  - Preclinical, CMC, clinical, project management

What is required to make the transition?

- Comprehensive Product Development Planning based on understanding of FDA regulations and expectations
- Effective communication with the FDA to assure concurrence with development plans
- Project management expertise to oversee execution of Product Development Plan
- Upper management support – Product development is a team effort and success is highly dependent on availability of appropriate resources and by upper management support

Product Development Phases

SPONSOR:



FDA:

30 Day Safety Review

Review amendments, annual reports, safety reports

8-12 Month Review (NME NDA/BLA)
6-10 Month Review (NDA)
12 Month Review (Biosimilar BLA)

Review Phase 4 study reports

Product Development Phases

- Discovery/Basic Research – (pre-IND)
  - No FDA Oversight – HOWEVER , failure to appreciate the regulatory requirements for future product development can result in significant delays when attempting to transition a product from the research lab to the clinic
- Process and Analytical Development (pre & post IND)
  - Process – Development & Optimization
    - Manufacturing consistency
  - Assays – Development & Specifications
    - Identity, Purity, Potency
    - Stability indicating
  - Drug Substance (Bulk Substance) and Drug Product Characterization

Product Development Phases

- Preclinical Animal Studies (pre-IND)
  - Proof-of-Concept
  - Toxicology
  - Safety Pharmacology
- IND Submission
- Clinical Trials
  - Phase 0, 1, 2 & 3
- Product Approval/Licensure
- Post-Marketing Studies (Phase 4)

Product Development Regulatory Goals

- Develop a reproducible process that can yield a consistent product and that can be run under GMPs
- Develop analytical procedures that can reliably measure product parameters, that are stability indicating, and can demonstrate product comparability following manufacturing/facility/equipment changes
- Develop animal models that can demonstrate proof-of concept and safety
- Demonstrate safety and efficacy in clinical trials

A Poor Regulatory Strategy Has a Significant, Negative Financial Impact

CAUSE

- Inadequate Animal Studies
- Inadequate Bench Testing
- Poor characterization
- Poor validation

- Clinical Study Delays
- Poor Enrollment
- Clinical Hold
- Clinical Supply Shortages

EFFECT

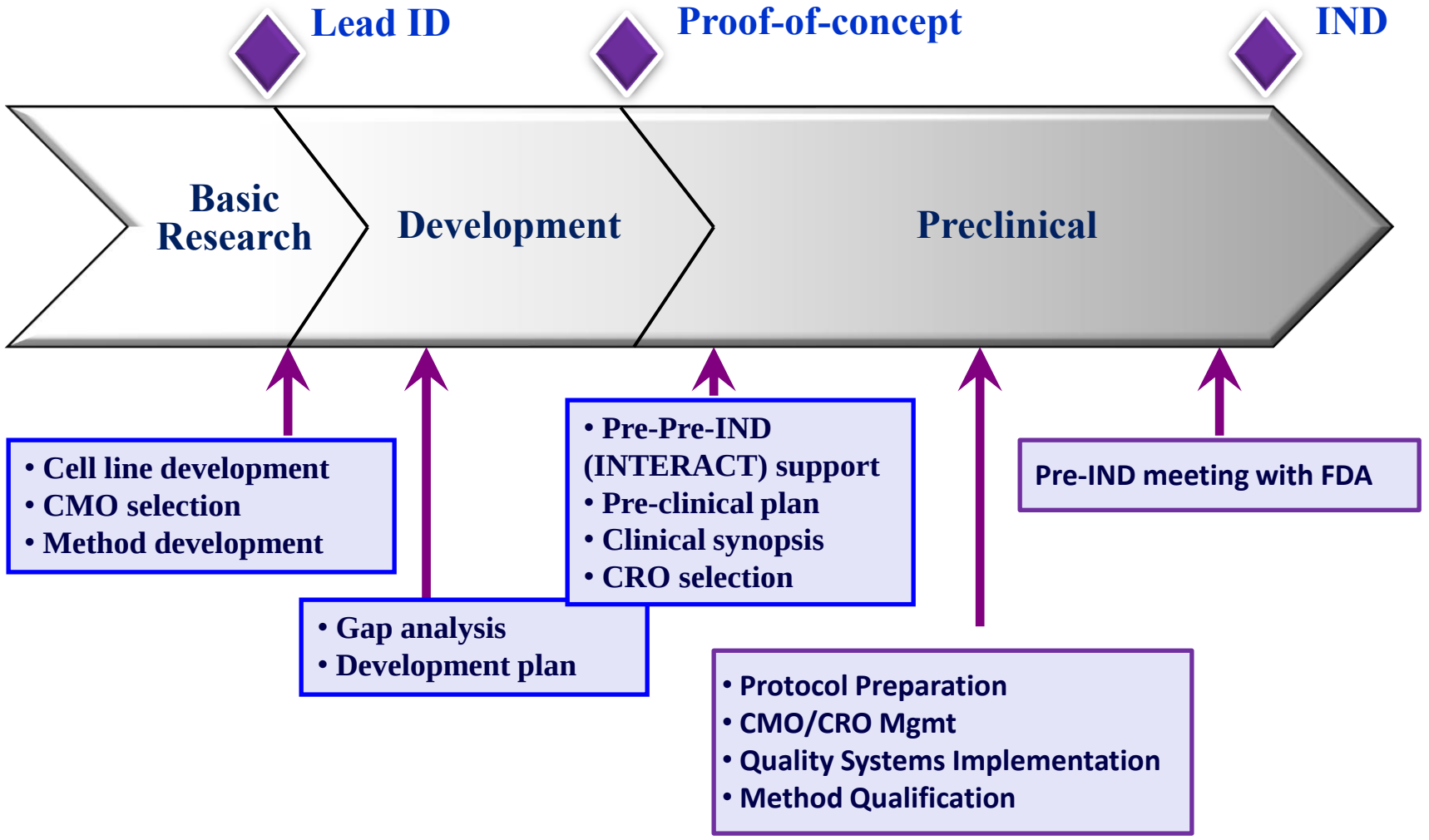
Private company:

- Shut the doors
- Bridge financing may be needed
- IPO/M&A less likely

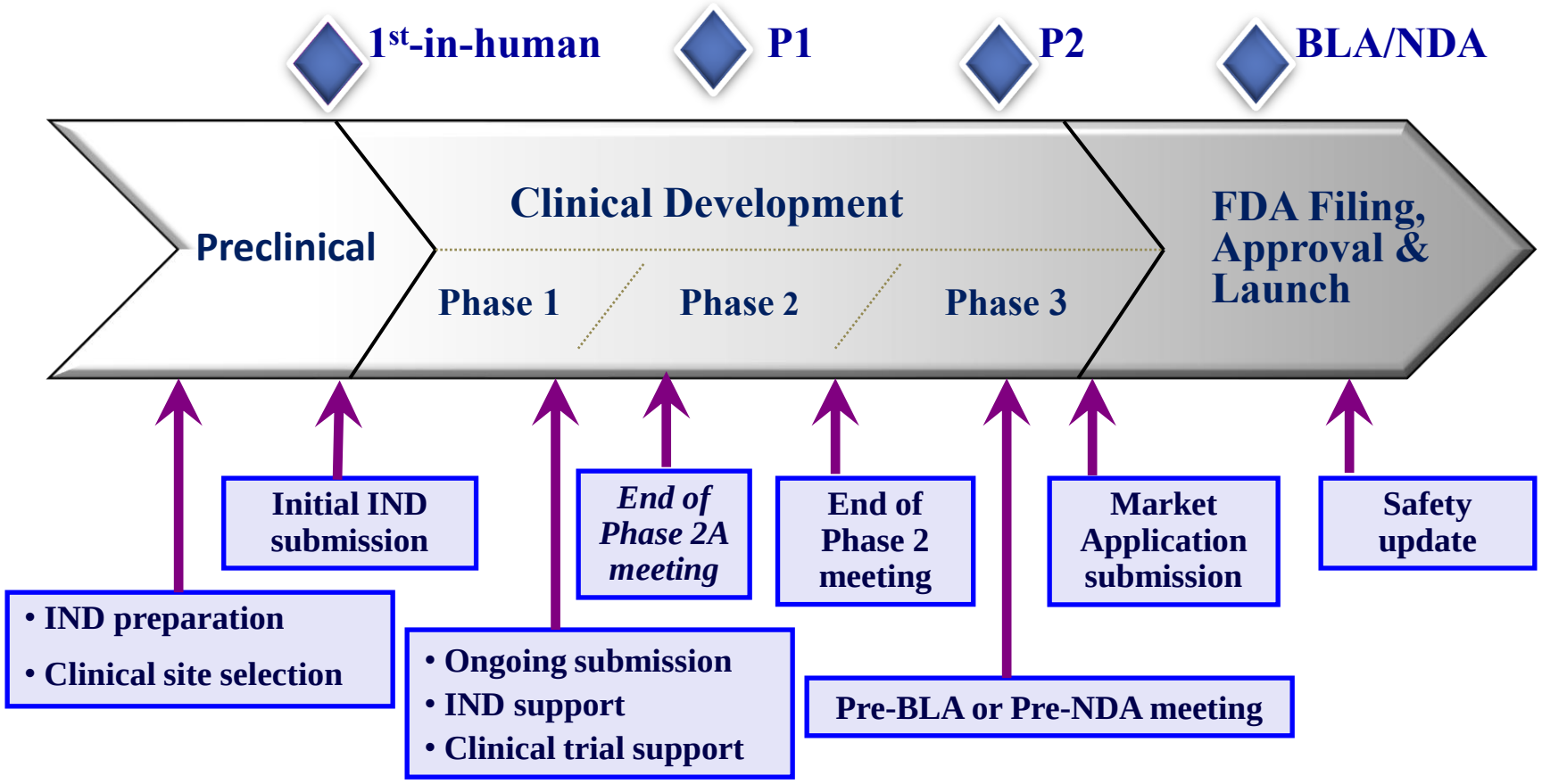
Public company:

- Decreased market cap
- Secondary offerings less likely
- Loss of confidence by public markets

Regulatory Affairs Impact
Key Early Development Milestones



Regulatory Affairs Impact
Key Clinical Development Milestones



FDA Expedited Review Pathways

Accelerated Approval

- Approval of drugs/biologics for serious conditions that fill an unmet medical need based on a surrogate endpoint.

Fast Track

- Review process designed to facilitate the development, and expedite the review of drugs to treat serious conditions and fill an unmet medical need.

Breakthrough Therapy

- A designation designed to expedite the development and review of drugs which may demonstrate substantial improvement over available therapy.

Priority Review

- A review designation whereby FDA's goal is to take action on an application within 6 months.

Regulatory interactions and requirements

- Informal advice from friends at FDA
- Consultants and advisors
- Guidelines – and there are many
- Formal meetings with regulatory agencies

US Regulatory Meetings

- Formalized program
- Guidance
- Some variation between review divisions

- INTERACT (aka Pre-Pre-IND)
- Pre-IND
- Post Phase 1 (End-of-Phase 1)
- Post Phase 2 (End-of-Phase 2)
- Pre Marketing Application (Pre-BLA, Pre-NDA)
- Others as needed

What can go wrong?

- Murphy’s law - What can go wrong will go wrong at the worst possible time.
  - But experience helps identify what should be done when and how
  - Cutting corners

- Manufacturing - GMP
- Preclinical Safety - GLP
- Clinical - GCP
- Regulatory

Manufacturing

- GMP
  - Some concessions for early clinical trials
  - Need a qualified experienced person to assess compliance requirements
- Manufacturing contractors
  - Compliance with GMP
  - Qualify contractors by audit
  - Monitor activities
- Examples of horror stories
  - Sterility tests on Master and Working Cell banks
  - Use of animal products
  - Poor documentation
  - Data integrity

Preclinical safety

- Contractors
- Compliance with GLP
- Need for monitoring
- Examples of what can go wrong
  - For cause audit
  - Poor sample handling
  - Contractor retested at their expense

Clinical

- Clinical Research Organizations (CROs)
- De-barred Investigators
- FDA audits
  - Falsification of qualifications
  - Source data verification
  - Not following inclusion/exclusion criteria
  - Adequate oversight of CRO by Sponsor
- Post hoc analysis of results

Good Regulatory Planning

- Understand your product
- Understand the regulatory expectations
- Develop the Product Development Plan with regulatory expectations in mind

- Check everything and everyone
- Get advice from independent experienced people early and often!

What is a Product Development Plan?

- A “roadmap” for your product’s development
- A concise, product-focused strategic document laying out the path to licensure/approval
- A detailed analysis of your product status and developmental requirements, including the four primary aspects of product development: Manufacturing, Preclinical, Regulatory and Clinical Development
- An integrated stand-alone document tying the four main areas of product development with budgets, tasks and timelines through Phase 1 or beyond

Typical PDP Content

- Background and Product Assessment
- Manufacturing Development Plan
- Preclinical Development Plan
- Clinical Development Plan
- Regulatory Development
- Project Management
- Budget
- Timelines

Biosimilar Products in the US

BPCI

- The Biologics Price Competition and Innovation Act of 2009 (BPCI Act) was passed as part of health reform (Affordable Care Act) that was signed into law on March 23, 2010
- BPCI Act creates an *abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with* an FDA-licensed reference product

Definition

Biosimilar or Biosimilarity means:

- that the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components; and
- there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product

Comparator Products

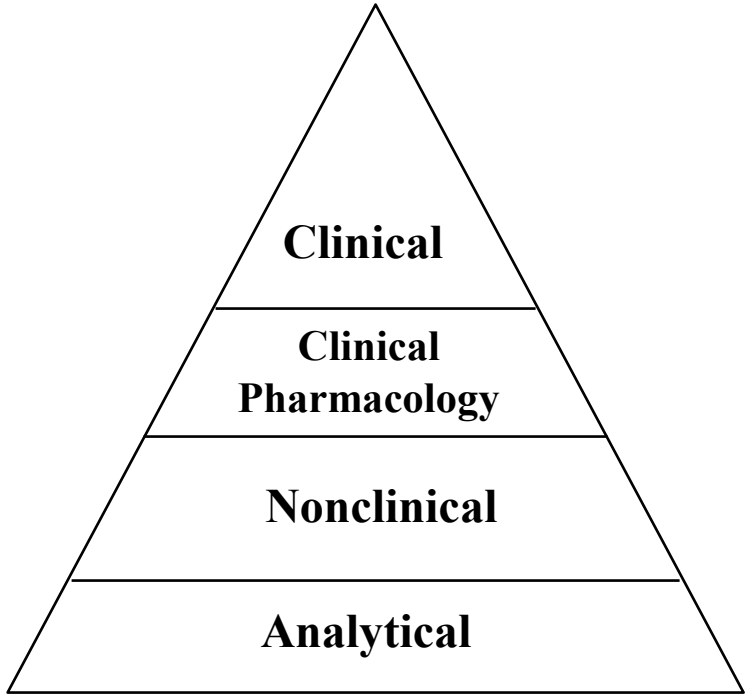
- The PHS Act defines the “reference product” for a 351(k) application as the “single biological product licensed under section 351(a) against which a biological product is evaluated.”
- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US licensed product may be used to support a demonstration of biosimilarity to a US-licensed reference product
- Adequate data or information should be provided to scientifically justify the relevance of these comparative data to an assessment of biosimilarity and to establish an acceptable bridge to the U.S.-licensed reference product

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is biosimilar to a reference product;
- Utilizes the same mechanism(s) of action for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- Condition(s) of use proposed in labeling have been previously approved for the reference product;
- Has the same route of administration, dosage form, and strength as the reference product; and
- Is manufactured, processed, packed, or held in a facility that meets standards designed to assure that the biological product continues to be safe, pure, and potent

Totality of Evidence



FDA will consider the totality of the data and information submitted in the application

FDA Approved Biosimilars

41 Approved, 27 Launched

Year	Number of Approvals	Interchangeable	Number Launched
2023	1		2
2022	7	2	4
2021	3	2	2
2020	4		6
2019	10		7
2018	7		3
2017	5		1
2016	3		1
2015	1		1

As of May 25, 2023

FDA Approved Biosimilars
(top 5)

Reference Product	Number of Biosimilars
Humira (adalimumab)	9
Neulasta (pegfilgrastim)	6
Herceptin (trastuzumab)	5
Avastin (bevacizumab)	4
Remicade (infliximab)	4

As of May 25, 2023

FDA Approved Interchangeable Biosimilars

Reference Product	Interchangeable Name	Year Approved
Lucentis (ranibizumab)	Cimerli [Coherus]	2022
Lantus (insuline glargine)	Rezvoglar [Lilly] Semglee [Viatris]	2022 2021
Humira (adalimumab)	Cyltezo [Boehringer Ingelheim]	2021

As of May 25, 2023

Summary

- Regulatory Compliance is Critical to Success
  - If the FDA does not approve it you cannot test it in humans and you cannot sell it
- Achieving Regulatory Compliance is not simple
  - It requires a significant dedication of resources by product development specialists who have expertise with your product type
- A Rigorous PDP will provide a roadmap to efficient development and speedy approval
- Biosimilar development pathway has legally been in place in the US since 2010 and has led to the licensure of 41 BLAs for biosimilar products, with 4 approved as interchangeable. Of those approved 27 have been launched.

Thank You

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